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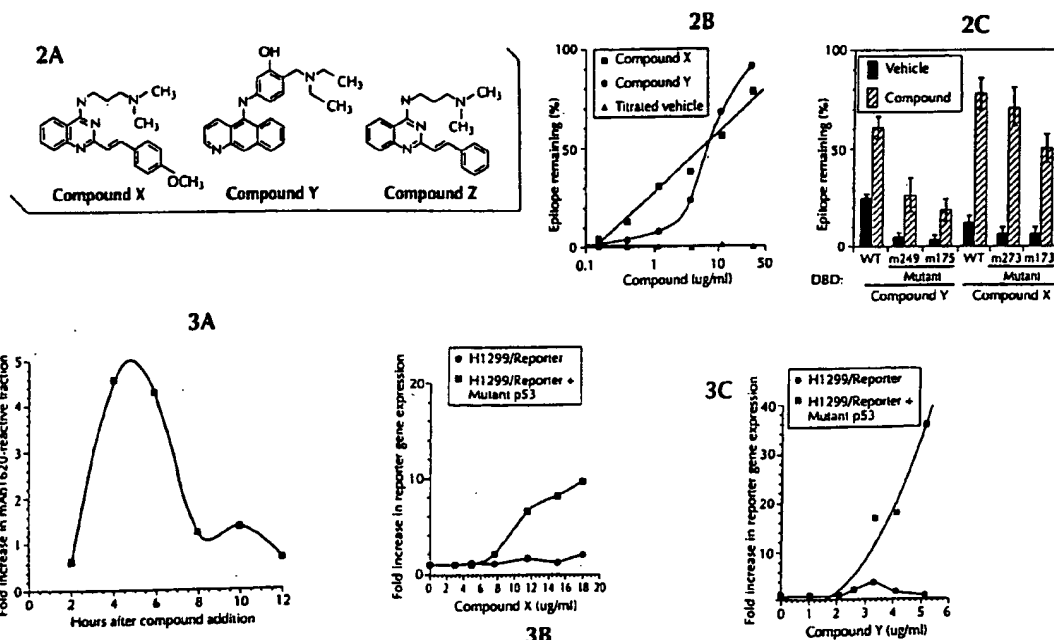
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/5415, 31/473, 31/496, 31/517, A61P 35/00, G01N 33/50		A3	(11) International Publication Number: WO 00/32175
			(43) International Publication Date: 8 June 2000 (08.06.00)
(21) International Application Number: PCT/IB99/01916		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 1 December 1999 (01.12.99)		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(30) Priority Data: 60/110,542 2 December 1998 (02.12.98) US			
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(74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).		(88) Date of publication of the international search report: 3 August 2000 (03.08.00)	

(54) Title: METHODS AND COMPOSITIONS FOR RESTORING CONFORMATIONAL STABILITY OF A PROTEIN OF THE p53 FAMILY



(57) Abstract

The invention provides pharmaceutical non-peptidic organic compounds capable of interacting with a functionally defective form of a mutant or a wild-type tumor suppressor protein of the p53 family (such as p53, p63 or p73). The interaction allows stabilization or folding of the protein in a functional conformation, thereby restoring all or part of its wild-type normal activity. More particularly said compounds interact with the DNA binding domain of p53 family proteins, are acridine, quinoline, quinazoline or phenothiazine derivatives, and are used in cancer therapy. Also provided are methods for screening such pharmacological compounds.

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INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/IB 99/01916

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5415 A61K31/473 A61K31/496 A61K31/517 A61P35/00
G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAINAUT ET AL.: "Redox modulation of p53 conformation and sequence DNA-binding in-vitro" CANCER RESEARCH, vol. 35, no. 18, 1 October 1993 (1993-10-01), pages 4469-4473, XP000891856 the whole document	1-3,5
Y	WO 94 12202 A (UNIVERSITY OF DUNDEE) 9 June 1994 (1994-06-09) see claims	1-3,5, 9-11,22, 23
A	page 32 -page 33, paragraph 1 see pages 7,8.12-16, 29 and 30 abstract	6,12,13, 16-19
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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A document member of the same patent family

Date of the actual completion of the international search

29 May 2000

Date of mailing of the international search report

07/06/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 99/01916

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOTOHASHI ET AL.: "Synthesis and antitumor activity of 1-(2-(chloroethyl)-3-(2-substituted-10H-ph enothiazin-10-yl)ALKYL-1! ureas as potent anticancer agents" ANTICANCER RESEARCH, vol. 16, no. 5a, 1996, pages 2525-2532, XP000901777 the whole document	17,20
A	GNIAZDOWSKI ET AL.: "Thiol-dependent inhibition of RNA synthesis in-vitro by acridines,. Structure-inhibition relationship" CANCER LETTERS, vol. 15, no. 1, 1982, pages 73-79, XP000901862 the whole document	17,20
A	WILSON ET AL.: "Hypoxia-selective antitumor agents. 2. Electronic effects of 4-substituents on the mechanisms of cytotoxicity and metabolic stability of nitracrine derivatives" J. MED. CHEM., vol. 32, no. 1, 1989, pages 31-38, XP000891841 see compound 15 page 34	24,25
P,A	HUPP ET AL.: "Regulation of p53 protein function through alterations in protein-folding pathways" CELL. MOL. LIFE SCI., vol. 55, no. 1, January 1999 (1999-01), pages 88-95, XP000891820 page 91, right-hand column -page 93, left-hand column	1-3,5,6, 9-13, 16-19, 22,23
P,A	OHNISHI ET AL.: "Restoration of mutant TP53 to normal TP53 function by glycerol as a chemical chaperone" RADIATION RES., vol. 151, no. 4, April 1999 (1999-04), pages 498-500, XP000904809 the whole document	1-3,5,6, 9-13, 16-19,23

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/01916

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 4 and 20 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Present claims 1-3,5-15,17-19,21-23 relate to compounds, methods and diseases defined by reference to desirable or undesirable characteristics and properties, namely:

- * compounds by being a "non-peptide compound", being "capable of binding to one or more domains of mutant p53 protein under physiological conditions and of stabilizing a functional conformation therein".

- * methods of "promoting wild-type activity in a mutant form of human protein of the p53 family, wherein one or more functional activities of said protein are at least partially impaired by the inability of said protein to maintain a functional conformation under physiological conditions".

- * "a disease state associated with possession of a mutant protein of the p53 family having one or more diminished wild-type activities".

The claims cover all compounds, methods and diseases having these characteristics and properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds/shods/apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds and methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of claims 24 and 25 and on therapy of cancer, with due regard to the general idea underlying the application.

CONCLUSION:

- Claims not searched : claims 1-23
- claims searched : claims 24 and 25 as far as relating to the therapy of cancer.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/IB 99/01916

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9412202 A	09-06-1994	AT 180673 T	15-06-1999
		AU 680216 B	24-07-1997
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